

Putting genomics into practice

A new analysis casts doubt on the clinical utility of *CYP2C19* genotype testing to help guide antiplatelet prescribing

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Variation in the human genome has long been considered to contribute to individual differences in disease susceptibility and drug response. But a key question for clinical practice is whether knowledge of a patient's genotype could be useful for stratifying disease risk or guiding treatment. In the linked systematic review Bauer and colleagues report a systematic review and meta-analysis of studies examining the association of variation in the *CYP2C19* gene and atherothrombotic events during treatment with clopidogrel.¹

The sequence of the human genome is now known,² as are the positions of the several million nucleotides that differ most commonly from one person to the next and their inheritance patterns in different human populations. Laboratory and analytical techniques now permit rapid cost effective direct (and indirect) genotyping of many single nucleotide polymorphisms (SNPs) in the genomes of many thousands of people to gain insight into the regions that influence disease related biomarkers, susceptibility to common diseases, or the response to widely prescribed drugs.

By 2011, nearly 1000 such genome-wide association studies had reported their findings (figure).³ Genome-wide association studies of disease risk are typically large and collaborative, and the results have usually been replicated in independent samples before publication. This means that the findings are not only among the most novel but also the most secure in any field of biomedicine. Although the precise causal genetic variants have yet to be defined with certainty in most cases, these studies have already provided early insights into disease pathogenesis that will probably yield future dividends in the form of new treatments.⁴

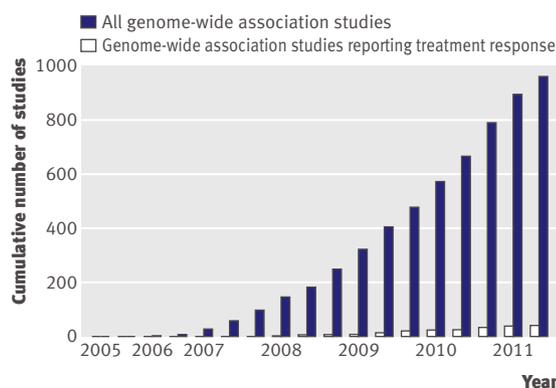
Unfortunately, information on common SNPs is proving less helpful for predicting disease risk than had been hoped⁵: the common genetic variants that have been studied so far have too

weak an effect. A panel of disease-associated SNPs may be more helpful for estimating risk at a group level, but only a minority of people in any population possess genomes with a large number of common risk variants. They are outnumbered by those with an intermediate number of common risk variants, who account for more of the cases, so even panels of SNPs associated with common diseases tend to perform poorly in distinguishing between those who will and will not become affected by a common disease.⁶ Rare genetic variants that are now being sought by high throughput DNA sequencing are predicted to have a larger effect on disease risk than common alleles.⁷ However, by their nature, few people in the population would harbour such variants, which reduces their usefulness for population-wide screening. Nevertheless, there is hope that rare, highly penetrant disease associated variants might provide an effective means of family based screening for certain disorders.

The area of personalised (or stratified) medicine, which is currently attracting substantial interest from industry, funders, and scientists, represents another potential application of the emerging genomic advances. Already, several established cancer treatments target cellular alterations caused by mutations or rearrangements in the genome of cancer cells.⁸⁻⁹ But, could inherited differences in drug response (pharmacogenetics)—mediated through alterations in the level or activity of proteins involved in absorption, metabolism, and elimination of drugs (pharmacokinetic-pharmacogenetics)—or the protein targets of drug action (pharmacodynamic-pharmacogenetics), help to predict treatment benefits and harms?

A few high profile examples illustrate the potential of pharmacogenetics (table; see bmj.com), but recommendations on the use of pharmacogenetic tests in clinical practice are often inconsistent. Moreover, a recent overview (covering pharmaco-genetic studies between 1967 and 2008) highlighted several problems in this field.¹⁰ These include a preponderance of reviews over primary research articles, underrepresentation of certain disease areas and ethnic groups, small sample sizes, a relative dearth of genome-wide association studies (figure); widespread use of surrogate outcome measures; and evidence of small study bias, of which publication bias is one cause. Poor study quality could delay the clinical development of valuable pharmacogenetic tests but also lead to premature adoption of poorly validated tests.

In their systematic review and meta-analysis, Bauer and colleagues evaluated the strength of evidence on the association between the variation in the *CYP2C19* gene and atherothrombotic events during treatment with clopidogrel.¹ Clopidogrel, a widely prescribed, now off-patent, antiplatelet agent (originally licensed as Plavix), requires metabolism for its activation. Several hepatic cytochrome enzymes contribute



Cumulative number of genome-wide association studies curated by the National Human Genome Research Institute (www.genome.gov/gwastudies)

▶ See more about healthcare in areas of conflict and violence on BMJ Group's crisis zone medicine page <http://bit.ly/e28arZ>

to this, including CYP2C19. There is an emerging view that people who carry reduced activity *CYP2C19* gene variants are less well protected from cardiovascular events during clopidogrel treatment and that genotype based tests could help inform decisions on the dose of clopidogrel, or whether to opt for newer more expensive (patented) antiplatelet drugs such as prasugrel or ticagrelor, which are considered less dependent on metabolism for their activation.

After several research articles on the association between *CYP2C19* genotype and response to clopidogrel, the US Food and Drug Administration (FDA) issued a boxed warning,¹¹ which notified clinicians “about reduced effectiveness in patients who are poor metabolizers of Plavix” and “that tests are available to identify genetic differences in *CYP2C19* function;” it also advised them “to consider use of other antiplatelet medications or alternative dosing strategies for Plavix in patients identified as poor metabolizers.”

The analysis by Bauer and colleagues has now unearthed evidence of small study bias in the literature relating to this area, with weakening of the overall association when more recent larger studies are added. The authors also identified inconsistencies between studies in relation to genotyping, study outcomes, and effect estimates that collectively question the validity of *CYP2C19* genotype testing to help guide antiplatelet treatment decisions.

The problems identified by Bauer and colleagues may not be unique to *CYP2C19* genotyping and clopidogrel response.¹² Efforts to strengthen the design, analysis, reporting, and appraisal of pharmacogenetic studies, drawing on experience from observational studies, gene-disease asso-

ciation studies, cancer biomarker studies, genetic tests as predictors of disease risk, and randomised trials, may now be needed to enable more efficient clinical translation of the emerging genomic discoveries.

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Delivering healthcare in situations of conflict or violence

The International Committee of the Red Cross sets out how to do it



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▶ Listen to a podcast about continuity of care in conflict situations with Geoff Loane, from the International Committee of the Red Cross, at bmj.com/podcasts

This week the International Committee of the Red Cross (ICRC) launches a global campaign—“It’s a matter of life and death”—which aims to improve security and delivery of effective and impartial healthcare in situations of armed conflict and other contexts of widespread violence.¹ This is timely. Events in Libya, Bahrain, Yemen, and elsewhere make it clear that when people take up arms for whatever reason, violence perpetrated against healthcare facilities and personnel is all too common.

In such contexts, healthcare is often suspended, withdrawn, or impossible. The wounded and sick are denied effective healthcare when hospitals are rendered non-functional by explosive force or forcibly entered by fighters; when ambulances are hijacked; and when healthcare personnel are killed, injured, threatened, kidnapped, or arrested for treating insurgents.

Ultimately, the ICRC campaign is about something intuitive to all health professionals who have worked in a context of conflict: that a secure environment is a prerequisite for the delivery of healthcare.² It is surprising that currently no mechanism exists for reporting violent events that affect healthcare.³

In a study of violent events affecting healthcare, the ICRC makes the case—and convincingly so—that insecurity of healthcare is one of the biggest, most immediate, and yet unrecognised humanitarian problems in today’s conflicts.⁴ Using all possible sources, the ICRC has collected and ana-

lysed reports pertaining to 655 violent events that have affected healthcare in 16 unnamed countries where it is operational. The study details the different types of perpetrator of violence, the means used by the perpetrators, who is affected, and in what way people are affected. The main findings ultimately relate to the nature of the threats to healthcare and the vulnerabilities of healthcare in the contexts concerned, and they are divided into three main categories (box).

The importance of the study goes beyond identifying the threats to healthcare and the vulnerabilities of healthcare. Each such incident will have a knock-on effect that constrains healthcare in some way for tens, hundreds, thousands, or even tens of thousands of people. In addition, as the authors point out, the study will have underestimated the number of and effect of such events. The methods used may have captured most major events, such as the killing or kidnapping of healthcare workers, but they will not have captured the thousands of small security events that, together, generate a climate in which it is impossible or at best difficult to deliver healthcare.

As a result of the study, the ICRC will actively promote appropriate measures to improve security and the delivery of healthcare in its entire field of operations. For example, hospitals and all those in them urgently need better protection from the effects of explosive force. Safeguards

Reports of violent events that have affected healthcare

Hospitals and other healthcare buildings

- Use of explosive weapons by state armed forces during active hostilities, which hit (intentionally or unintentionally) healthcare infrastructure, and at the same time kill and injure people
- Armed entry into healthcare infrastructure by state actors (state armed forces and police), with the principal purpose of arrest or interrogation of the wounded and sick
- Armed entry into or takeover of healthcare infrastructure by armed groups to harass personnel, to steal materials, or to occupy the buildings or vehicles for their own medical or tactical purposes

Healthcare transportation

- Attacks on healthcare vehicles and personnel en route by state armed forces or armed groups
- Damage to ambulances caused by state armed forces and to a lesser extent armed groups using improvised explosive devices
- Harassment and delay of ambulances or other vehicles transporting wounded or sick people at checkpoints by state armed forces and police

Healthcare personnel

- Use of explosive weapons by state armed forces during active hostilities that results in death and injury
- Kidnapping of healthcare personnel from their place of work by armed groups
- Killing of expatriate healthcare personnel by armed groups
- Arrests of healthcare personnel
- Threats by a variety of actors (usually representatives of governments, insurgents, or similar groups)

must be put in place to deter armed entry into any healthcare facilities. State armed forces must be better trained to organise and manage checkpoints so that ambulances are given rapid and unhindered passage.

These measures clearly do not lie within the health community but principally in the domain of law, politics, humanitarian dialogue, and operating procedures of military bodies.

The motor for action outside the health community is routine, consistent, and credible information gathering about violent events that affect healthcare. The acknowledgement of the problem and the governmental interest shown at the World Health Assembly in May of this year is encouraging.⁵

The ICRC's study and work highlights two broad roles for the health community. Firstly, healthcare professionals who are likely to be working in insecure environments must have adequate training on how medical ethics apply in these different and difficult circumstances. Secondly, there is a need to build a community of concern that goes beyond the health community to those who are in a position to ensure security of healthcare in places and situations where they are most needed.

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Antidepressants in older people

Carefully monitor for adverse effects, particularly in the first month



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Because older people with clinical depression have high rates of concurrent medical illness, particularly cerebrovascular disease, they are at high risk of adverse events from most antidepressants.¹ However, given the likelihood of poor functional outcomes and the increased risk of premature death by suicide, vascular disease, accident, or injury, safe and effective interventions are needed.¹⁻³ In the linked cohort study, Coupland and colleagues assess the association between antidepressant treatment and risk of adverse outcomes in older people with depression in primary care.⁴

Although the relative benefits of new antidepressants are clearer than they once were⁶ there are still valid concerns about prescribing to younger⁷ and older patients. Although the reduction in suicide with the use of antidepressants is evident in older people,⁸ it has been harder to determine whether increased prescribing may also cause harm.

Coupland and colleagues assessed the effects of antidepressants in 60 706 patients aged 65 and over with a newly diagnosed episode of depression.⁴ Importantly, patients in this large primary care based cohort had the typical high rate of medical comorbidity. Although the authors highlight the limitations of their observational research, the study has clear implications for more informed prescribing and enhanced clinical monitoring.

All classes of antidepressant drugs were associated with increased risks of adverse events, and there were important differences in the type and frequency of serious effects across the various therapeutic classes. All of the SSRIs were associ-

ated with an increased risk of falls (hazard ratio 1.66, 95% confidence interval 1.58 to 1.73), and citalopram, escitalopram, and fluoxetine were also associated with hyponatraemia (1.52, 1.33 to 1.75). Trazodone, mirtazapine, and venlafaxine were associated with higher risks of all cause mortality and several potentially life threatening events, including attempted suicide or self harm and stroke or transient ischaemic attack.

The data show that the prescription of low dose tricyclic antidepressants remains popular—at least in the United Kingdom (31.6% of all antidepressant prescriptions). Unexpectedly, low dose tricyclic antidepressants did not have the highest hazard ratio for any of the adverse outcomes reported. However, for all the associations reported, important interactions between unknown patient factors and drug choice could still have occurred.

Certainly, venlafaxine is typically used in those with more severe or treatment resistant depression (which may be indicative of extensive medical comorbidity). Both trazodone and mirtazapine are more likely to be prescribed to patients with serious sleep disturbance or agitation, factors that again are often linked with more serious physical ill health. As the dose of tricyclic antidepressants increased, the risks of all cause mortality, falls, seizures, and fractures increased. For most adverse outcomes, the high risk periods were during the month after starting or stopping antidepressants.

The authors did not look at the extent to which antidepressant prescribing is used to treat other related symptoms such as headache, chronic pain, or sleep disturbance. Given the potential

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harms,^{9 10} the decision to prescribe for an older person with depression should not be taken lightly.

From a practice perspective, the high rate of prescribing described in the linked study (almost 90%) is noteworthy. Other data indicate that family practitioners prescribe psychoactive compounds to between one third and two thirds of people who present with psychological disorders.^{11 12} Although it seems that prescribing is reserved for more severe cases, or those who have failed to respond to psychological treatments, we need to be clearer that drugs should not be recommended as first line treatments for less severe depressive disorders, particularly in older patients.

The low rate of use of non-drug based treatments alone in this study has important implications for interpretation of these comparative analyses. These patients formed the “control” group but comprised only 10% of available subjects. A more clinically relevant approach may have been to use those people who received SSRIs as the control group (55% of the sample), because this group is most consistent with other standard clinical guidelines for persons with at least moderately severe depression.^{6 9} Future studies from this database, and other large health services resources, may be more clinically useful if they choose control groups that are representative of typical clinical practice. The database emphasises that for older people with at least moderately severe depression or other predictors of a likely response to drugs, the first line choice should remain those SSRIs that have the best ratio of benefits to harm (notably sertraline and citalopram).^{1 6 9 10} Although it is not necessary to seek a specialist opinion before starting treatment, clinicians, including those in primary care, need to be aware of the special circumstances surrounding the prescription of antidepressants to older people with depression (such as undetected cerebro-vascular comorbidity, frequency and types of adverse events that can be life threatening).¹ Older people therefore require careful monitoring for adverse effects, with provision

of information (to the patient and carer) about the risks of falls, confusion, agitation, and increased suicidal ideation. They should also be advised that adverse effects are most commonly encountered during the first few weeks of treatment.^{1 4} For this reason, patients should be monitored at least weekly during the first month of treatment and again when drugs are stopped.⁴ Independently of the severity of depression or the prescription of drugs, all patients should be provided with appropriate psychological support and advice about behavioural interventions—particularly those aimed at increasing their daily activity and improving their sleeping patterns.^{1 9 10}

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Misoprostol for management of postpartum haemorrhage

No benefit if oxytocin is available, but useful where no other alternatives exist

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For decades, oxytocin and ergometrine have been the treatments of choice for postpartum haemorrhage caused by ineffective uterine contraction (uterine atony). Although both drugs are effective, oxytocin is more widely used because it has fewer side effects and can be used safely in women with hypertension and pre-eclampsia. However, in their usual form both drugs can be given only by injection, and both require refrigeration. They are therefore of limited availability and benefit in low resource settings, especially in rural areas. Misoprostol, an orally active and heat stable prostaglandin E₁ analogue, has therefore emerged as a popular alternative. Until a year ago, there was limited evidence for its ability to treat postpartum haemorrhage.^{1 2} However proponents have argued that it should be “parachuted in” to high risk areas despite the lack of evidence.³ This, in part, has been responsible for its inclusion in multiple guidelines on postpartum haemorrhage both in rich and poor settings (despite the call in a systematic review for more studies²).

Since the systematic review of the treatment of postpartum haemorrhage was last updated in 2007,² three large double

blind randomised trials have been published.⁴⁻⁶ Few research teams had been able to carry out a randomised trial of treatment for this condition, but Gynuity Health Projects and the World Health Organization, with backing from the Bill and Melinda Gates Foundation, were able to recruit more than 80 000 women in 14 centres worldwide to three trials to define the role of misoprostol. Although these trials are impressive, they have gone largely unnoticed by many maternity care workers.

The first compared 800 µg sublingual misoprostol with 40 IU oxytocin given in a litre of intravenous solution over 15 minutes for the treatment of postpartum haemorrhage in women who had not received oxytocin prophylaxis.⁴ The study recruited 9348 subjects; 10% of them were diagnosed with postpartum haemorrhage (around 700 mL of blood loss) and received the study treatments. Further bleeding of at least 300 mL (1 L total) occurred in 30% of the women given misoprostol and in only 17% of women given oxytocin (relative risk 1.78, 95% confidence interval 1.40 to 2.26). Misoprostol was associated with more side effects—“intolerable shivering” was seen in 11% of women receiving misoprostol compared

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Discuss post partum haemorrhage on BMJ Group's obstetrics and gynaecology forum <http://bit.ly/qqpCuO>

with less than 1% of women taking oxytocin (55.2, 7.70 to 397).

The second trial used the same protocol but in those women who had received routine prophylaxis with oxytocin.⁵ Evidence of the benefit of prophylaxis with oxytocin was overwhelming—only 3% (809/31 055) of women bled compared with 10% in the trial above where no prophylaxis was available. In this second trial, additional blood loss of 300 mL or more after treatment was similar in the two groups (34% v 31%; 1.12, 0.92 to 1.37), whereas blood loss of more than 1 L after treatment occurred in 11 (3%) women managed with misoprostol and three (1%) women given oxytocin (3.62, 1.02 to 12.89). Intolerable shivering occurred in 4% and less than 1% of women treated with misoprostol and oxytocin respectively (16.8, 2.25 to 125). These findings suggest that 800 µg sublingual misoprostol is a possible alternative to 40 IU intravenous oxytocin for the management of postpartum haemorrhage after prophylactic oxytocin, but that it does have more side effects.

The third study assessed the effect of using misoprostol in addition to conventional injectable uterotonics to treat postpartum haemorrhage.⁶ The study compared 600 µg sublingual misoprostol to placebo in 1422 women who were being treated with 10 IU intramuscular or slow intravenous oxytocin for the treatment of postpartum haemorrhage. The study found no significant difference between the two treatment groups in the proportion with blood loss of 500 mL or more within 60 minutes (14% in both treatment groups; 1.02, 0.79 to 1.32) or blood loss greater than 1000 mL (1% in both treatment groups; 1.02, 0.41 to 2.55). Consistent with the other trials, side effects were more common with misoprostol than with placebo.

Following on from WHO studies nearly 10 years ago showing that misoprostol was less effective than oxytocin for prophylaxis,⁷ the results of these studies were disappointing for misoprostol enthusiasts. Not only is it less effective than oxytocin, but it has more side effects and no adjunctive effect if the woman has already been given oxytocin. The only comfort is that detailed examination of the data, along with the excellent outcomes for the participants, suggests that misoprostol is better than nothing.

So is there any remaining role for misoprostol in the management of postpartum haemorrhage? In settings where

oxytocin is freely available it should be used instead of misoprostol for prophylaxis. And although the two drugs have similar efficacy after oxytocin prophylaxis, there is no benefit of providing a second drug that is commonly more expensive, has more side effects, and has no additional effect.

In rural low resource settings, however, where injectable oxytocics are rarely available, misoprostol is an important weapon in the fight against postpartum haemorrhage related mortality. Its heat stability and ease of use mean that all midwives and doctors in these settings should carry a stock. Furthermore, recent observational studies in women having home births in Nepal and Afghanistan suggest that giving misoprostol to women antenatally for self administration immediately after delivery may be a safe and effective strategy.^{8,9} A large placebo controlled randomised trial is now under way to test this hypothesis. If true, this would provide an effective self administered treatment for the first time to those women most at risk of death from postpartum haemorrhage, and it could help reduce maternal mortality worldwide.

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How family friendly is the UK?

The UK is lagging behind the rest of the EU on several measures of family wellbeing

Before becoming prime minister, David Cameron promised voters he had a “long term vision of making Britain the most family friendly country in the world,” and now *The Family Pressure Gauge*, published in May 2011, is an attempt by the Relationships Foundation to measure Cameron's annual progress in “helping families with the pressures they face.”¹ This pressure gauge compares official data from the United Kingdom with other European countries. Overall, Britain is judged a bad place to be a child (table).¹

Policies that promote a secure family home, a safe school environment, parents' escape from poverty, and inclusion in local social networks contribute towards maximising the potential wellbeing of every child.² Unfortunately for population health and wellbeing, millions of British children do not experience such positive environments. In 2007, a

Unicef report showed that life was miserable for more schoolchildren in the UK than in other “economically advanced” nations.³ It took a while for the Department of Health fully to grasp the implications of this widespread family misery, but a 2011 strategy prioritised the prevention of mental illness and early intervention for childhood problems.⁴ The strategy also committed the Department of Health to work alongside the Office for National Statistics in developing better measures of wellbeing and the Office for Civil Society in linking social policy more directly to wellbeing. These partners agreed that wellbeing included individual, family, and neighbourhood dimensions. At the level of primary healthcare, all these dimensions can arise simultaneously—for example, in developing a local children's centre.⁵ This overlap is important for future collaborative clinical commissioning and the provision

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of new services (such as basing health visiting within local authority services).

The Relationships Foundation’s report aims to focus the attention of policy makers on various pressures now experienced by families in the United Kingdom by showing that the UK scores badly, compared with other European countries, on a composite measure. Across 27 countries with overall scores ranging from the best in Norway (pressure only 0.235) to the worst in Romania (pressure 0.524) the UK finishes 24th out of 27, with a score of 0.477. No units are given for the measures on this apparent continuum, which is based on a convenience sample of 25 indicators (“the closest proxies for the Conservative manifesto”), which are unweighted, arbitrarily grouped into four key domains, ranked within the domains, and then reconstituted within the “average” overall score. Although the gauge is based on a wide variety of data, it contains no statistical analysis, which implies that the authors aimed to impress politicians with an avalanche of data, rather than interpret those data to inform specific policies.

There are several difficulties in interpreting the validity of the score. For example, because the score comprises a composite of several unweighted indicators, it is impossible to tell whether the score represents a small proportion of the population with a large number of pressures or a more even spread. Unicef showed that the poorest 10% of UK children who have the least chances in life experience extreme inequalities in resources for education, such as no space at home where they can sit down to do their homework.⁶ Health inequalities reflect multiple pressures on some families—for example, births to women aged 15-19 is an indicator where the UK ranks 26th out of 27.¹ Any realistic policies around teenage pregnancy have to account for deep inequalities; an example would be targeting public health outreach to girls in care.⁷

The Relationships Foundation’s report also shows that the UK has the highest proportion of children living in workless households in the EU, and highlights several areas that threaten family health, such as the burden of household debt on parents (rank 27/27) and adolescents who get drunk repeatedly (rank 25/27). The report cites five factors that lead to poverty: family breakdown, economic dependency and worklessness, educational failure, addiction, and personal indebtedness. Yet for some reason the public health community has failed to translate these concerns into effective action.⁸ These pathways are convergent, not independent, as politicians would discover if they listened to young people’s concerns about the social environments in which they now grow up.⁹ Often young people shrug off specific health risks from their excessive drinking but at the same time express their concern about the bleakness of their life chances.

What needs to happen to improve these rankings? Their publication alone is unlikely to be enough. Nonetheless, if enough

health and social care commissioners are stimulated to think again about what makes families flourish,² and the new collaborative health and wellbeing boards that link local health and social services can integrate input from many experienced professionals, family health might benefit from 2012 onwards.

The Relationships Foundation closes its report with a consultation, and it invites a “conversation” about family friendliness during 2011. There is a list of other measures that might be relevant, such as providing more green spaces. The United Nations Educational, Scientific and Cultural Organization presented a plan to parliament on new green landscapes for a civil society,¹⁰ and many parents would welcome more family friendly parks and gardens to enjoy with their children. The consultation ends by seeking some measurable outcome of family friendly policy. This could be a measure of shared resilience within a community. All children experience pressure, but resilience involves “knitting” individual stories into wider connections with people and communities.¹¹ In relation to *No Health Without Mental Health*,⁴ the crucial nature of these connections between individual children and their local social environment has been discussed with Lord Wei and other advisers on the government’s proposed “Big Society” initiative. The big society may have a very short life unless that resilience, rooted across generations and neighbours, promotes the solidarity and altruism needed for it to grow. The minister for decentralisation and cities views “the grace of undiluted altruism” as a vital strand of the big society (www.communities.gov.uk/speeches/corporate/growingbigsociety) but we have yet to see how the planned 5000 community organisers will sustain that strand, if times are hard.

What can the UK learn from other countries that score highly on family wellbeing? In the Netherlands, vulnerable families and communities are monitored over time, with the aim of making effective early interventions that can be coordinated locally. Unsurprisingly, the indices of teenage births and adolescent drunkenness are much lower in the Netherlands than in the UK.¹ But this is part of a wider Dutch policy of supporting families. For example, compared with the UK, in the Netherlands more adults are able to adopt flexible working hours (34.9% v 21.4%) and far fewer children experience severe housing deprivation (0.4% v 4.8%).¹

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Areas where the UK falls far behind the best other European countries¹

Indicator	UK percentage	Percentage in lower “pressure” countries
Population living in households with very low work intensity	12.6	Iceland 2.1; Switzerland 3.4
Children experiencing severe housing deprivation	4.8	Netherlands 0.4; Finland 0.6
Births to women aged 15-19 years	2.6	Switzerland 0.5; Denmark 0.6
Children in households with debt >100% of monthly disposable income	13.9	Finland 0.9; Norway 1.0
15 year olds who have been drunk at least twice	47.4	Malta 17.6; Greece 19.1